General

Guideline Title

Guidelines for the diagnosis and management of adult myelodysplastic syndromes.

Bibliographic Source(s)

Killick SB, Carter C, Culligan D, Dalley C, Das-Gupta E, Drummond M, Enright H, Jones GL, Kell J, Mills J, Mufti G, Parker J, Raj K, Sternberg A, Vyas P, Bowen D, British Committee for Standards in Haematology. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. Br J Haematol. 2014 Feb;164(4):503-25. [144 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A–C) and strength of recommendations (Strong [Grade 1], Weak [Grade 2]) are given at the end of the "Major Recommendations" field.

Diagnosis

1. Myelodysplastic syndrome (MDS) should be suspected in patients with otherwise unexplained cytopenia(s) or macrocytosis (Grade 1A).
2. The initial assessment of a patient with unexplained cytopenia(s) may not confirm a diagnosis of MDS. Further follow-up and reassessment may be necessary to reach a firm diagnosis (Grade 2B, C).
3. Initial assessment of a patient with suspected MDS should include a minimum set of investigations and the differential diagnosis of marrow dysplasia should be considered (Grade 1A).
4. Patients with MDS should be assessed by a haematologist and, except where clearly inappropriate, offered review by a regional or national expert given the disease rarity.
5. All cases of MDS should be classified according to the World Health Organization (WHO) Revised Classification 2008 (Grade 1A).
6. Bone marrow cytogenetic analysis should be performed on all patients with suspected MDS having a bone marrow examination (Grade 1A).
7. Consideration should be given at diagnosis to the prognosis for each individual patient, with application of the revised International Prognostic Scoring System (IPSS-R) (Grade 1B).
8. All cases of MDS should be reported to the National Cancer Registry and MDS-specific registries if applicable.

Supportive Care

1. Supportive care should be the mainstay for all patients with MDS and symptomatic cytopenias (Grade 1A).

2. Blood transfusions should be given to improve symptomatic anaemia (Grade 1A).
3. A trigger haemoglobin concentration cannot be recommended for all patients; it should be individualized (Grade 1A).
4. Extended red cell phenotyping should be considered for patients receiving regular red cell transfusions (Grade 2C).
5. Routine platelet transfusions should not be given to stable, non-bleeding patients who are not receiving intensive chemotherapy (Grade 1A).
6. Local policies should be in place for the management of neutropenic sepsis (Grade 1A).
7. Emotional health needs should be continually assessed and addressed. Disease-specific information should be re-iterated regularly.

Iron Chelation

1. Iron chelation therapy cannot be routinely recommended for MDS patients with transfusional iron overload (Grade 1C).
2. Consideration may be given to chelation therapy for patients with a very good prognosis, specifically patients with WHO refractory anaemia (RA), RA with ringed sideroblasts (RARS) and isolated del(5q). Triggers may include more than 20 units of red cells transfused, serum ferritin >1000 μg/l in patients for whom continuing red cell transfusion is predicted (Grade 2C).
3. Patients treated with iron chelation therapy should ideally receive this treatment within clinical trials.
4. Desferrioxamine remains the therapy of choice with the longest record of safety and efficacy of all three agents available. Deferasirox is recommended for patients intolerant of desferrioxamine. Deferiprone could be considered in patients with normal baseline neutrophil counts (Grade 2C).

Growth Factors

1. Patients with IPSS low and intermediate-1 (INT-1) MDS, symptomatic anaemia and who fulfil the criteria for a high or intermediate predictive score for response should be considered for a trial of therapy with an erythroid-stimulating agent (ESA) (Grade 1B).
2. Patients with non-sideroblastic phenotypes should be offered a trial of therapy with an ESA (Grade 1B).
3. Patients with sideroblastic phenotypes should be offered a trial of therapy with an ESA plus granulocyte colony-stimulating factor (G-CSF) (Grade 1B).
4. Patients should receive a maximum trial period of 16 weeks of therapy. This should comprise 8 weeks at the starting dose of ESA± G-CSF and a further 8 weeks at the higher doses, if required (Grade 2B).
5. Patients achieving a complete or partial erythroid response by accepted criteria should continue on long-term therapy until the response is lost and at the minimum dose of ESAs required to maintain the response (Grade 2B).
6. The haemoglobin concentration should not be allowed to rise above 120 g/l (Grade 2C).

Immunosuppression

Immunosuppressive therapy with antithymocyte globulin (ATG) (horse ATG, currently available as ATGAM, Pfizer, New York, NY, USA) can be recommended in suitable low or INT-1 IPSS MDS patients who are typically less than 60 years of age and have a normal karyotype or trisomy 8 (Grade 2C).

Lenalidomide

1. Patients with IPSS low or INT-1 MDS with del(5q), symptomatic anaemia and who fulfil the criteria for a high or intermediate predictive score for response, should be first considered for a trial of ESA therapy (Grade 1B).
2. For transfusion-dependent patients unsuitable for a trial of ESA, or for non-responders/patients losing their response to ESA, who have IPSS low or INT-1 MDS with del(5q), consider treatment with lenalidomide 10 mg daily for 21 days repeated every 28 days (Grade 1B). A careful discussion with patients about the risk and benefit is mandatory.
3. Selected MDS patients with del(5q) and IPSS low/INT-1 may be candidates for allogeneic stem cell transplantation. These include lenalidomide-treated patients who fail to achieve transfusion independence, those losing their response, or patients with transfusion dependence not considered suitable for lenalidomide (Grade 2B).
4. Lenalidomide is not currently recommended for patients with del(5q) and bone marrow blasts >5%, multiple (complex) cytogenetic abnormalities in addition to del(5q), patients with IPSS INT-2/high or with a known mutated *TP53* gene (Grade 2B).

Allogeneic Transplant for Low-Risk Disease

1. Clinicians should discuss all patients eligible for stem cell transplantation with their local transplant unit and each case should be assessed on its own merits (Grade 2B).
2. Consideration should be given to the European Group for Blood and Marrow Transplantation (EBMT) risk score, which has been validated for MDS, and the Haematopoietic Cell Transplantation Comorbidity Index (HCT-CI) (Grade 2B).
3. Consideration should also be given to additional prognostic features, such as red cell transfusion dependence, which can profoundly

influence the prognosis in patients eligible for transplant (Grade 2B).
4. Current data suggest that transplants from matched unrelated donors can have similar outcomes to those from matched sibling donors (Grade 2B).
5. Myeloablative conditioning regimens are recommended over reduced intensity conditioning (RIC) regimens when they can be delivered safely (Grade 2C).

Chronic Myelomonocytic Leukaemia (CMML)

1. Supportive care ± hydroxycarbamide as required is recommended for most patients (Grade 1B).
2. Azacitidine is licensed for non-proliferative CMML-2 and can reasonably be recommended (Grade 2C).
3. Allogeneic haematopoietic stem cell transplantation (HSCT) with or without preceding acute myeloid leukaemia (AML)-type chemotherapy should be considered for selected patients (Grade 2B).
4. Patients requiring treatment should be considered for any appropriate clinical trial.

High-Risk Patients Eligible for Allogeneic Transplant

1. Early allogeneic stem cell transplantation with or without prior AML-type induction chemotherapy should be considered for eligible patients with high-risk MDS (Grade 2B).
2. Eligibility for stem cell transplantation should be based on HCT-CI and performance status rather than age (Grade 2B).
3. Patients with a low comorbidity score (HCT-CI <3) should be considered for allogeneic stem cell transplantation. The role of transplantation in those patients with a high comorbidity score is unclear (Grade 2B).
4. Patients with >10% blasts should receive 1 to 2 courses of intensive chemotherapy to induce remission prior to transplantation (Grade 2B).
5. It is recommended that serum ferritin be measured pretransplant for additional predictive information (Grade 2B).
6. Matched unrelated donor transplants are recommended where a sibling donor is unsuitable or unavailable (Grade 2B).
7. Intensity of conditioning depends on the 'risk' of the disease and patient factors (Grade 2B).
8. Patients who fail to respond to pre-transplant induction therapy should not undergo allogeneic stem cell transplantation and should be considered for experimental therapy or supportive care alone (Grade 2B).
9. Autologous stem cell transplantation for MDS is not recommended outside of clinical trials (Grade 2B).

High-Risk Patients Not Eligible for Allogeneic Transplant

1. In fit older patients lacking an adverse karyotype, the options of azacitidine versus intensive chemotherapy should be carefully discussed. Standard regimens used in *de novo* AML should be used as intensive chemotherapy in eligible patients (Grade 2B).
2. Azacitidine is recommended as first-line therapy for patients ineligible for a stem cell transplant with IPSS INT-2 and high-risk MDS, CMML-2 or AML with 20% to 30% blasts (Grade 1A).
3. The recommended dose of azacitidine is 75 mg/m^2 daily for seven consecutive days but a 5-2-2 schedule is acceptable where it is not practical to offer seven consecutive days (Grade 2B).
4. Responding patients should continue azacitidine until their response is lost (Grade 1A).
5. The decision to stop or continue azacitidine in patients who fail to achieve a response after six cycles, but who have stable disease, is dependent upon clinician and patient preference (Grade 2B).

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose–response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current

evidence from observational studies, case series or just opinion.

Strength of Recommendations

Strong (Grade 1): Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as "recommend".

Weak (Grade 2): Where the magnitude of benefit or not is less certain a weaker Grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as "suggest".

Clinical Algorithm(s)

The following algorithms can be found in the original guideline document:

- Algorithm for management of low-risk myelodysplastic syndrome
- Algorithm for management of high-risk myelodysplastic syndrome

Scope

Disease/Condition(s)

Myelodysplastic syndromes (MDS)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Hematology

Internal Medicine

Medical Genetics

Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide healthcare professionals with clear guidance on the management of patients with myelodysplastic syndrome (MDS)

Target Population

Patients with myelodysplastic syndrome (MDS)

Interventions and Practices Considered

Diagnosis/Evaluation

1. Assessment for myelodysplastic syndrome (MDS) in cases of unexplained cytopenia(s) or macrocytosis
2. Further follow-up after initial assessment may be needed to confirm diagnosis of MDS
3. Minimum set of investigations and consideration of differential diagnosis
4. Classification of MDS according to the World Health Organization (WHO) Revised Classification 2008
5. Bone marrow cytogenetic analysis
6. Application of the revised International Prognostic Scoring System (IPSS-R)
7. Reporting all cases of MDS to the National Cancer Registry and MDS-specific registries if applicable

Management/Treatment

1. Supportive care
    - Individualized haemoglobin concentration
    - Blood transfusions to improve symptomatic anaemia
    - Extended red cell phenotyping for patients receiving regular red cell transfusions
    - Platelet transfusions (not recommended for stable, non-bleeding patients who are not receiving intensive chemotherapy)
    - Management of neutropenic sepsis
    - Consideration of emotional health needs
2. Iron chelation therapy (desferrioxamine, deferasirox, deferiprone)
3. Growth factors
    - Erythroid-stimulating agent (ESA) with or without granulocyte colony-stimulating factor (G-CSF)
    - Maintenance of haemoglobin concentration below 120 g/l if using an ESA
4. Immunosuppression therapy with antithymocyte globulin (ATG)
5. Lenalidomide
6. Allogeneic stem cell transplantation
    - Consideration of the European Group for Blood and Marrow Transplantation (EBMT) risk score, and the Haematopoietic Cell Transplantation Comorbidity Index (HCT-CI)
    - Consideration of additional prognostic features such as red cell transfusion dependence
    - Consideration of myeloablative conditioning regimens over reduced intensity conditioning (RIC) regimens
7. Management of chronic myelomonocytic leukaemia (CMML)
    - Supportive care ± hydroxycarbamide
    - Azacitidine
    - Allogeneic haematopoietic stem cell transplantation (HSCT) with or without preceding acute myeloid leukaemia (AML)-type chemotherapy
    - Consideration for appropriate clinical trials

Major Outcomes Considered

- Survival rate
- Overall response rate
- Acute myeloid leukaemia (AML) transformation rate
- 5-year post-transplant relapse rates
- Remission rates
- Morbidity and mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Recommendations are based on review of the literature using MEDLINE and PubMed up to December 2012 under the heading: "myelodysplastic syndrome".

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose–response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Levels of evidence and grades of recommendation have been assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature for assessing the quality of evidence and providing strength of recommendations (see the "Rating Scheme for the Strength of the Evidence" and the "Rating Scheme for the Strength of the Recommendations" fields).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline group was selected to be representative of UK-based myelodysplastic syndrome (MDS) medical experts.

The writing group produced the draft guideline, which was subsequently revised with consensus by members of the Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (Grade 1): Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as "recommend".

Weak (Grade 2): Where the magnitude of benefit or not is less certain a weaker Grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as "suggest".

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of approximately 50 United Kingdom (UK) haematologists, the British Committee for Standards in Haematology (BCSH) and the British Society for Haematology Committee. Comments were incorporated where appropriate.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for most of the recommendations (see the "Major Recommendations" field.)

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate and accurate diagnosis and management of adults with myelodysplastic syndrome (MDS)

Potential Harms

- Chronic red cell transfusion may lead to complications including iron overload and the development of red cell alloantibodies.

- Intensive chemotherapy related complications (e.g., marrow aplasia, infection and haemorrhage)
- Older patients frequently have co-morbidities, making intensive regimens less well tolerated.
- Only half of all patients complete 1 year of deferasirox therapy, most due to non-treatment related adverse events. The U.S. Food and Drug Administration (FDA) has added a black box warning to the label for deferasirox for enhanced vigilance with renal impairment, hepatic impairment and gastrointestinal haemorrhage.
- Toxicities such as neutropenia and thrombocytopenia are side effects of lenalidomide. Other groups have reported an increased risk of secondary malignancies with lenalidomide in myeloma.

Contraindications

Contraindications

Patients with higher risk myelodysplastic syndrome (MDS) are generally not considered for therapy with erythroid-stimulating agents (ESA) because of poor responses, short survival times and the increasing use of hypomethylating agents and stem cell transplantation, which require red cell transfusion support.

Qualifying Statements

Qualifying Statements

- While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.
- The guidance may not be appropriate to every patient and in all cases individual patient circumstances may dictate an alternative approach.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Killick SB, Carter C, Culligan D, Dalley C, Das-Gupta E, Drummond M, Enright H, Jones GL, Kell J, Mills J, Mufti G, Parker J, Raj K, Sternberg A, Vyas P, Bowen D, British Committee for Standards in Haematology. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. Br J Haematol. 2014 Feb;164(4):503-25. [144 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Feb

Guideline Developer(s)

British Society for Haematology Guidelines - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

British Committee for Standards in Haematology (BCSH) Writing Group

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Financial Disclosures/Conflicts of Interest

The British Committee for Standards in Haematology wishes to declare that AS, DB, S Killick, S Kell, HE, KR, ED, CD, JM, MD and DC have

been in receipt of educational grants, research funding, speaker's fees and/or consulting fees from Celgene, Amgen, Novartis, Pharmion, Roche, Chugai and/or Jansen-Cilag. In addition, DB has attended advisory boards for Amgen, S Kell for Celgene, ED for Johnson & Johnson and DC for Roche, GSK, Celgene and Novartis. PV, GJ, GM, CC and JP have no conflicts of interest to declare. Full details of all disclosures can be obtained by contacting the British Society for Haematology.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the British Journal of Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on April 30, 2014. The information was verified by the guideline developer on May 28, 2014.

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